Comparative Analysis of Immune and Viral Dynamics in Infant and Adult Rhesus Macaques

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Abstract

Prevention of vertical HIV transmission and HIV in infants will require further efforts than just antiretroviral treatment [1]. Understanding viral dynamics in infants in relation to that of adults will provide valuable insight as to new methods of treatment [5]. Our model uses data collected from rhesus macaques (RM) infants and adults infected with SHIV.CH505.375H.dCT, an SIV variant with HIV behavior. This paper is solely focused on the behavior during acute infection of HIV, which in this case is the first 8 weeks of infection. We create a nondimensionalized immune control model as to decrease the number of parameters being estimated with limited observations, in addition to a normal immune control model. The models fitted to both infant and adult data showed various similarities and differences between HIV development. This nondimensionalized model is used as a means for comparison between infant and adults, rather than a tool to estimate each model parameter. This specific parameter estimation is completed through the normal immune control model.

1 Introduction

Vertical (mother to child) transmission of HIV continues to cause roughly 150,000 infant infections annually [8], resulting in nearly a million children living with HIV worldwide. It is extremely challenging to prevent vertical transmission using antiretroviral therapy (ART)-based measures, and novel strategies for pediatric HIV prevention are urgently needed [6]. This project is part of a larger experimental/modeling research effort to understand the immune mechanisms that determine the acquisition and control of Simian HIV (SHIV) in infant Rhesus macaques and develop new therapies. This work will develop the first part of a series of models, with others modeling the dynamics during ART and different immunotherapies, as well as following treatment interruption. In this project, we will fit an immune control model of acute infection to viral load data from the first 8 weeks post-infection with SHIV. While such models have been studied previously in adult Rhesus macaques and human subjects, there is little data available for infants, who have an immature and yet rapidly developing immune system that may impact viral acquisition and control. By comparing our infant RM models to adult RM models, we hope to provide insight into how viral and immune dynamics are similar to or different from adults [4] [7].

2 Methods

2.1 Data

Data was provided by Dr. Ria Goswami at Duke Human Vaccine Institute [3]. Type D Retrovirus, Simian Immunodeficiency virus (SIV) , and Simian T cell leukemia virus type 1(STLV-1)-free Indian rhesus macaques (RM) (Macaca mulatta) were used for this study. This method acts as a control to ensure that all RMs are uninfected prior to experiment. Six infant RMs were orally challenged with SHIV.CH505.375H.dCT at 4 weeks of age 3 times a day for 5 days, to mimic breast milk transmission. After 1 week, 1 infant RM became infected. The rest of the macaques were sedated and then challenged orally at a higher dose until infected. After 10 weeks, all RMs were infected with the virus. Six adult RMs, ranging from 4 to 10 years of age, were intravenously infected with the same strain of SHIV. Plasma viral RNA load of the RMs was assessed using a highly sensitive quantitative reverse transcription PCR (qRT-PCR) assay. The sensitivity of this assay was 15 copies of vRNA/mL plasma.

2.2 Immune Control Model

The model used is called Immune Control Model as presented by Perelson et.al [2] and is a system of differential equations. The model is defined as follows:

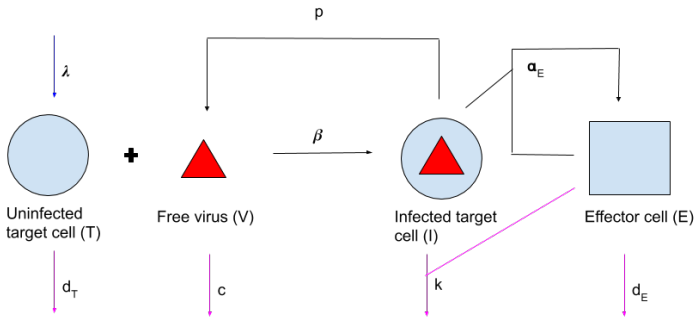

Figure 1: System of Differential Equations described by the diagram above

$$\frac{dT}{dt} = \lambda - d_T T - \beta VT$$
$$\frac{dI}{dt} = \beta VT - kIE$$
$$\frac{dV}{dt} = pI - cV$$
$$\frac{dE}{dt} = \alpha_E IE - d_E E$$

Where the variables used are defined such that T is the uninfected target (CD4) cell count, I is the infected cell count, V is the viral load, E is the effector cell (Killer T cell) count, and t is the time in weeks. The parameters are defined such that λ is the rate of production of T cells, d_T is the natural death rate of T cells, β is the rate at which T cells become infected cells, k is the rate at which infected cells are killed by effector cells, p is the rate of production of virus from infected cells, c is the natural clearance rate of the virus from the body, α_E is the rate at which effector cells are produced, and d_E is the natural death rate of effector cells.

2.2.1 Nondimensionalized (ND) Model

Data for viral load during acute infection was given with 9 observations, once a week. The current immune control model being used requires that 8 parameters are to be estimated. To reduce the number of parameters that need to be estimated, we now nondimensionalize our current model.

For convenience of notation during nondimensionalization, we now define the immune control model as:

$$\frac{dx}{dt} = \lambda - d_T x - \beta v x$$

$$\frac{di}{dt} = \beta v x - kie$$

$$\frac{dv}{dt} = pi - cv$$

$$\frac{de}{dt} = \alpha_E ie - d_E e$$

Where the changed variables are defined such that:

x is the T (CD4) cell count, previously T
i is the infected cell count, previously I
v is the viral load, previously V
e is the effector cell (Killer T cell) count and, previously E
t is the time

To ensure that all variables and parameters have the same resulting units after nondimensionalization, the current units of each variable and parameter are given as:

Parameter/Variable	Units
x	cells
i	cells
v	viral concentration (vconc)
e	cells
t	weeks
λ	$\frac{cells}{week}$
d_T	$\frac{1}{week}$
β	$\frac{1}{vconc*week}$
k	$\frac{1}{cells*week}$
p	$\frac{vconc}{cells*week}$
c	$\frac{1}{week}$
α_E	$\frac{1}{cells*week}$
d_E	$\frac{1}{week}$

To nondimensionalize this system, we first redefine the original model as products of a new dimensionless variable (e.g. x^*) and a scaling parameter (e.g. X) that has the same units as the original variable (e.g. x).

$$x = x^* X,\ i = i^* I,\ v = v^* V,\ e = e^* E$$

Substituting the rescaled variables into the system and simplifying:

$$\frac{dx^*}{dt^*} = \frac{\lambda T}{X} - d_T x^* T - \beta V T v^* x^*$$

$$\frac{di^*}{dt^*} = \frac{\beta V T X v^* x^*}{I} - kETi^* e^*$$

$$\frac{dv^*}{dt^*} = \frac{pITi^*}{V} - cTv^*$$

$$\frac{de^*}{dt^*} = \alpha_E ITi^* e^* - d_E Te^*$$

Now we define the scaling parameters X, I, V, E, and T with values that simplify our model, keeping the units the same.

Let $T = \frac{1}{d_T}$, $X = \frac{\lambda}{d_T}$, $V = \frac{d_T}{\beta}$, $I = \frac{d_T}{\alpha_E}$, and $E = \frac{d_T}{k}$:

$$\frac{dx^*}{dt^*} = 1 - x^* - v^* x^*$$

$$\frac{di^*}{dt^*} = \frac{\lambda \alpha_E v^* x^*}{{d_T}^2} - i^* e^*$$

$$\frac{dv^*}{dt^*} = \frac{p\beta i^*}{\alpha_E d_T} - \frac{cv^*}{d_T}$$

$$\frac{de^*}{dt^*} = i^* e^* - \frac{d_E e^*}{d_T}$$

Thus, our simplified dimensionless model is:

$$\frac{dx^*}{dt^*} = 1 - x^* - v^* x^*$$

$$\frac{di^*}{dt^*} = a' x^* v^* - i^* e^*$$

$$\frac{dv^*}{dt^*} = b' i^* - c' v^*$$

$$\frac{de^*}{dt^*} = i^* e^* - d' e^*$$

where $a' = \frac{\lambda \alpha_E}{{d_T}^2}$, $b' = \frac{p\beta}{\alpha_E d_T}$, $c' = \frac{c}{d_T}$, $d' = \frac{d_E}{d_T}$

Our simplified model now has 4 dimensionless parameters compared to the original 8 parameters with units.

2.2.2 Model Fitting

The model fitting is completed in R using package - Flexible Modeling Environment (FME) - that models ordinary and partial differential equations using non-linear least squares. Parameters are given initial values to predict around. Function modCost evaluates residuals of model output and raw data. Function modFit uses the output of modCost to find the best-fit parameters.

3 Results

3.1 Data

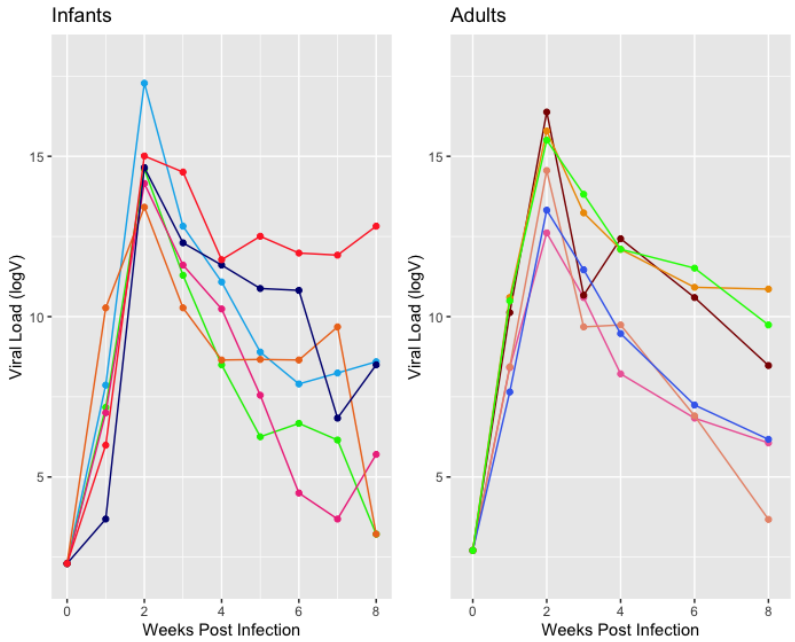

Figure 2: Plot of raw infant and adult RM data of viral load.

Values of viral load are presented in form log(V) for best visualization of differences in data. Each different color is a RM subject and each point is an observation.

3.2 Model Analysis

The following three pairs of graphs are the normal immune control and nondimensionalized models fitted to the data of three different infant RMs, which are described in the figure legends. All three normal immune control model graphs show a better fit than that of the nondimensionalized

model graphs. This indicates that parameters given from the normal graphs are more accurate in describing the behavior of the virus.

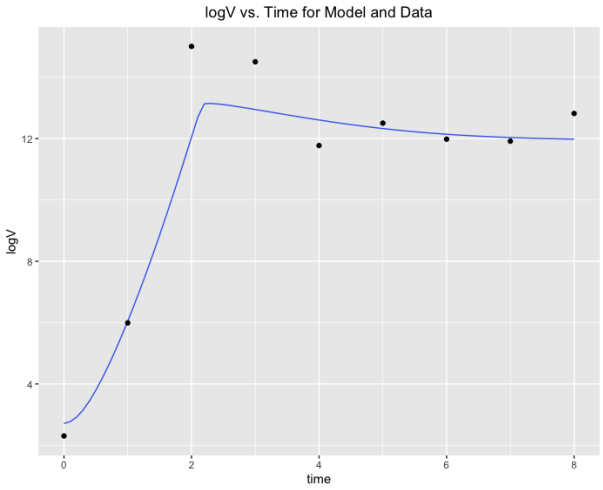

Figure 1. Immune control model fitted to raw data for infant RM46352. Credit: D. Fang

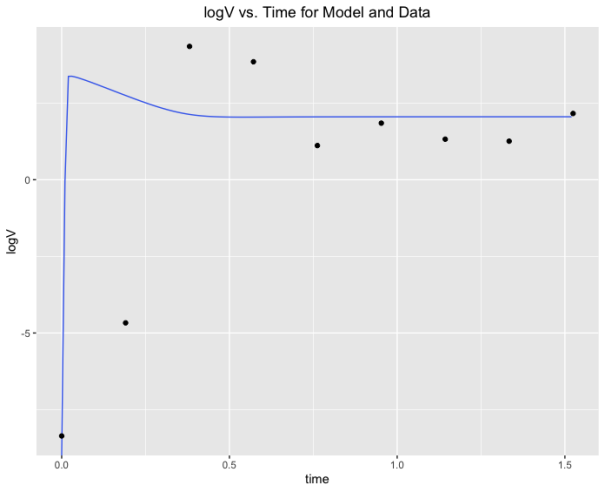

Figure 2. Nondimensionalized form of fitted immune control model for infant RM46352. Credit: D. Fang

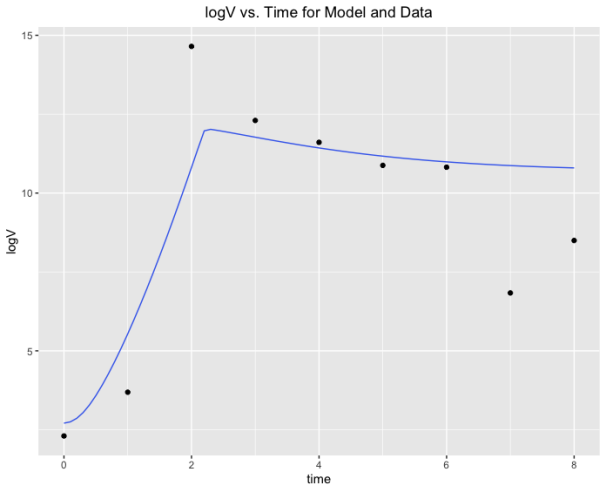

Figure 3. Immune control model fitted to raw data for infant RM46357. Credit: D. Fang

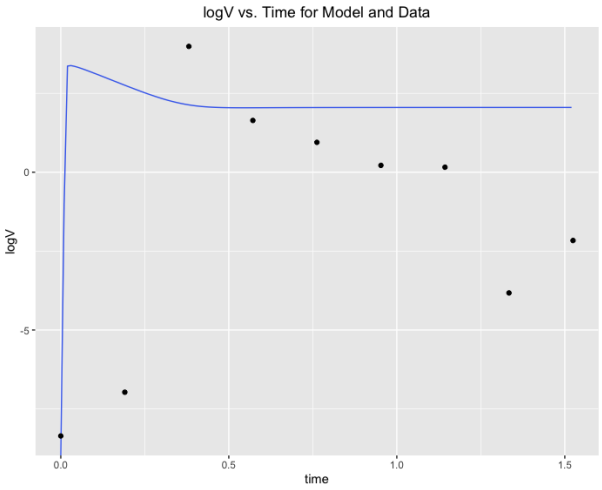

Figure 4. Nondimensionalized form of fitted immune control model for infant RM46357. Credit: D. Fang

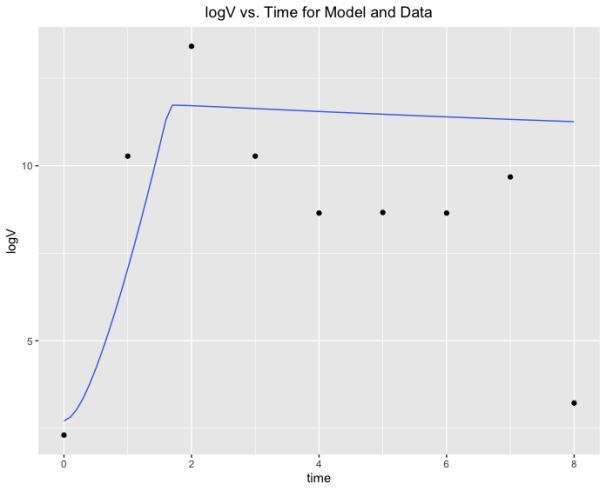

Figure 5. Immune control model fitted to raw data for infant RM46380. Credit: D. Fang

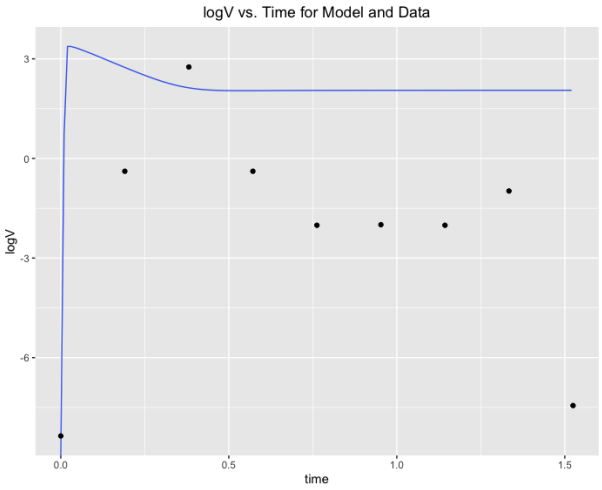

Figure 6. Nondimensionalized form of fitted immune control model for infant RM46380. Credit: D. Fang

The following two pairs of graphs depict the normal immune control and nondimensionalized models for 2 different adult RMs, which are identified in the figure legends.

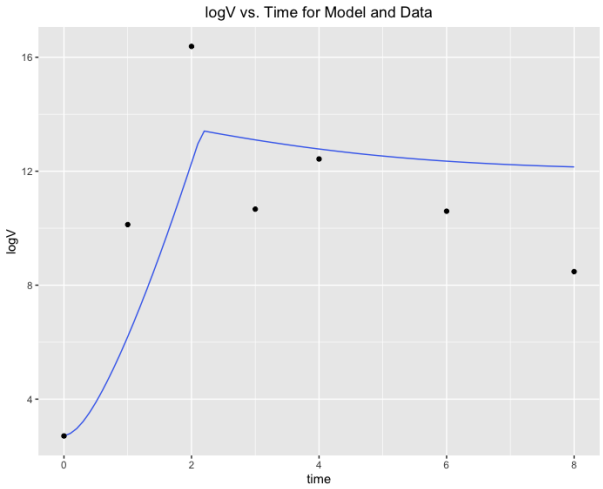

Figure 7. Immune control model fitted to raw data for adult RM A48270. Credit: D. Fang

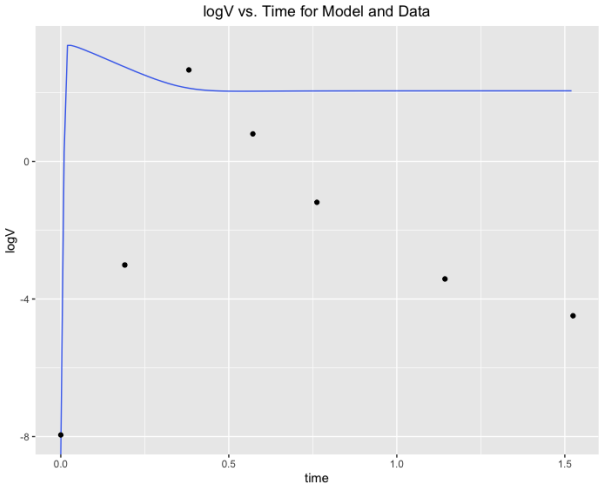

Figure 8. Nondimensionalized form of fitted immune control model for adult RM A48270. Credit: D. Fang

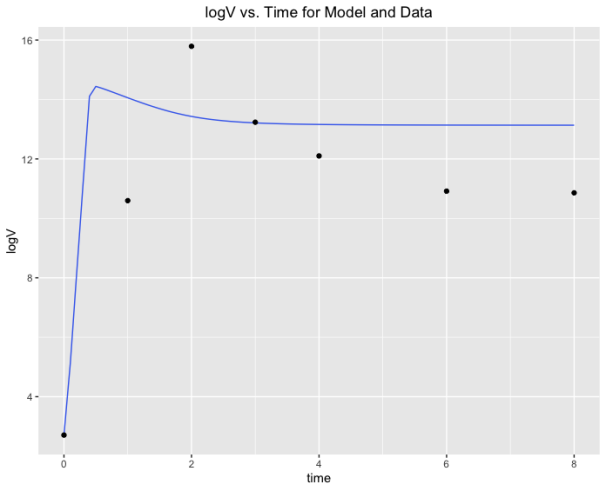

Figure 9. Immune control model fitted to raw data for adult RM A39472. Credit: D. Fang

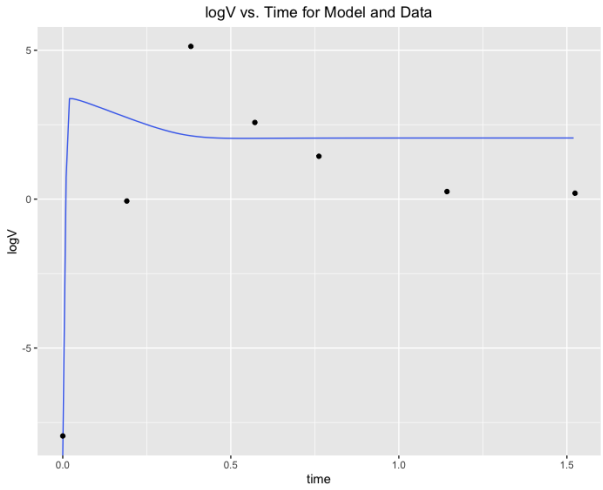

Figure 10. Nondimensionalized form of fitted immune control model for adult RM A39472. Credit: D. Fang

3.3 Fitted Model Parameters

The parameters that were fitted for the nondimensionalized parameters are as follows:

Parameter	Infants	Adults
λ	354.81	402.039
d_T	0.190546	0.22357
β	0.000014467	0.000015938
k	0.000001	0.00000234
p	14439.12	13762.386
c	0.5173521	0.5219307
α_E	1.200	2.102938
d_E	2.585710	1.983726

The following are the resulting means of the parameters fitted from the nondimensionalized model for both infants and adults. Parameters have no units because of the nondimensionalization completed in previous steps. Comparisons of both normal and nondimensionalized parameters will be discussed in the following section.

ND Parameter	Infants	Adults
a'	49695.913137	50029.32938
b'	3000	2318
c'	39.718788	46.27364
d'	12.680227	53.394827

3.4 Parameter Comparisons

Infant effector cells are produced at a much slower rate than those of adult effector cells. Additionally, infant effector cells die at a much faster rate than those of adult effector cells. These values are biologically accurate since infant immune systems are still developing and thus have weaker, slower producing effector cells. Furthermore, other parameters, such as production of target cells, death rate of target cells, production of virus particles, and creation of infected cells are relatively similar between infants and adults. This is reflective of biological expectations since developing immune systems don't have effects on the target and infected cell production and death rates.

These differences and similarities between infant and adult immune systems in RMs allows for better understanding of infant interactions with SHIV and thus HIV. Through comparisons to adult RM models, we have gained a deeper understanding of the viral and immune dynamics of infant RMs. We hope that this information can be used to further the knowledge on HIV in infants.

4 Conclusion

Parameters for infant Rhesus macaques differ from those for adult Rhesus macaques when considered with a Immune Control Model. From this we can conclude that infant immune systems in RMs interact differently to SHIV than that of adult RMs during the acute phase of infection in some ways. These being the production and death of immune system cells. Yet, in other ways, infant RMs interact similar to adult RMs do to SHIV. Further steps should be taken to refine the model for the analysis of other periods of SHIV development under ART and post ART, rebound stage.

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